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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/064,000	04/21/1998	JAMES P. ELIA	796-P-12	5311

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *382--405* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *382-405* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment of 03 November 2006 has been entered. The letter of 25 September 2006 (including exhibits A-E, G-I, K and L) has been entered.

Claims 382-405 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 382-402 under 35 U.S.C. § 112, first paragraph, regarding new matter as set forth at p. 11 of the previous Office Action (mailed 22 September 2006) is withdrawn in view of the amended claims (submitted with the amendment received 03 November 2006).

The objection to claims 385-388, 390, and 392 under 37 CFR 1.75(c) as being of improper dependent form as set forth at p.12 of the previous Office Action (mailed 22 September 2006) is withdrawn in view of the amended claims (submitted with the amendment received 03 November 2006).

35 U.S.C. § 112, Second Paragraph

Claims 383, 384, 391, 393, and 394 remain rejected under 35 U.S.C. § 112, second paragraph, for reasons of record.

Applicant's arguments (pp. 7-23, amendment received 03 November 2006) have been fully considered but are not found to be persuasive for the following reasons.

Applicant reiterates previous arguments that the examiner erred in substituting her opinion for that of a previous examiner. This has been fully considered but is not found persuasive because several pieces of evidence have been discussed in making and maintaining this rejection. Thus, the rejection is based on evidence, not mere opinion.

Applicant argues that the previous examiner's assumed understanding of the term as well as the declarations by highly skilled physicians constitute evidence that the terms are understood. This is not found to be persuasive. The declarations have been addressed previously. The rejection is maintained based upon the preponderance of the totality of the evidence.

Applicant refers to patent 5,759,033 and exhibits A and B of the amendment of 26 June 2006 as evidence supporting their position. These pieces of evidence have already been addressed.

Applicant argues that it is inconsistent for the examiner to understand the term with respect to proteins or genes but not to cells, since Applicant intends the term "growth factor" to include all three. This has been fully considered but is not found to be persuasive. The term "multifactorial and nonspecific" simply is not used in the art to describe cells. No evidence has been brought forth to establish otherwise. The specification does not use the term to describe cells specifically. Evidence has been brought forth to support the rejection. Therefore, the rejection is properly maintained.

Applicant again addresses the findings in Philips v. AWH Corporation. This is not found to be persuasive for reasons of record.

Applicant argues that the examiner has ignored applicant's searches and inappropriately performed searches in areas not related to the claimed invention. This has been fully considered but is not found to be persuasive. All of the evidence brought forth by applicant has been addressed. The examiner's search was performed to respond to applicant's numerous requests for evidence. The preponderance of the totality of the evidence supports the rejection.

Applicant argues that whether or not the terms encompass cells other than stem cells and germinal cells in not relevant, as stem cells and germinal cells are exemplary. This has been fully considered but is not found to be persuasive. The claims recite "cells" without further description (e.g., cl. 382), cells that are "multifactorial and non-specific" (e.g., cl. 383), a subgenus of cells that are "multifactorial and non-specific" that further comprise "stem cells" (e.g., cl. 384), cells that comprise "stem cells" (e.g., cl. 389), cells that comprise "pluripotent cells"(e.g., cl. 391), a subgenus of cells comprising "pluripotent cells" that further comprise "stem cells" (e.g., cl. 393), and a further subgenus of cells comprising "pluripotent cells" that also comprise "stem cells" wherein the stem cells are "multifactorial and non-specific" (e.g., cl. 394). Different claims are presumably presented to define different scopes of patent protection based upon these terms. 35 U.S.C. § 112, second paragraph requires Applicant to provide claims that particular point out and distinctly claim the subject matter which the Applicant regards as his invention. For the reasons of record, the metes and bounds of all of these

subsets of claims cannot be determined because there is no clear definition of "multifactorial and non-specific cells," and because the claims contradictorily imply that "multifactorial and non-specific cells" are both broader and more narrow than the term "stem cells." Therefore, the claims to not particularly point out and distinctly claim the subject matter which the applicant regards as his invention, and the claims fail to meet the requirements of 35 U.S.C. § 112, second paragraph.

Applicant takes issue with the examiner's questioning of the term "cascade of genetic material" by providing evidence in exhibits B and C. Applicant reasons that if the examiner cannot understand such an allegedly basic medical term, then she has not foundation upon which to question the term "multifactorial and non-specific." This has been fully considered but is not found to be persuasive. The terms "angiogenic cascade" and "genetic cascade" are NOT the same as the term "cascade of genetic *material*." Thus the evidence in exhibits B and C does not support applicant's position.

Applicant again takes issue with the examiner's search results, and again points to evidence in the fifth supplemental IDS, NIH Medical Dictionary, Merriam Webster's Medline Plus Medical Dictionary, and the declarations of Drs. Heuser and Lorincz. This has been fully considered but is not found to be persuasive. All of this evidence has been addressed on the record.

At pp. 16-17 of the response, Applicant argues that stem cells and germinal cells are exemplary of multifactorial and non-specific cells, along with pluripotent and bone marrow stem cells. This has been fully considered but is not found to be persuasive. The specification does not appear to support the assertion that pluripotent cells are also

considered to be part of the genus defined by "multifactorial and non-specific cells." Bone marrow stem cells are a type of stem cells and do not further illustrate the metes and bounds of the term at issue.

Applicant again refers to Strauer 2005 as supporting their position. Applicant characterizes the examiner's treatment of Strauer 2005 as allegedly acknowledging that the definition is applied to cells. This has been fully considered but is not found to be persuasive. To be clear, it is the examiner's position that Strauer 2005 does NOT further clarify what is meant by the term "multifactorial and non-specific cells." As explained in the previous Office Action, Strauer 2005 uses "four mechanisms" to describe "regenerative potential," not cells *per se*.

Applicant again points to Caplan 2001 as supporting their position. This has been fully considered but is not found to be persuasive for reasons of record.

Applicant points to the sixth supplemental IDS which lists Caplan 1991. Applicant also quotes from Caplan 1991 to support their position. This has been fully considered but is not found to be persuasive. Caplan 1991 discusses factors that affect the behavior of a cell. However, it would appear that the behavior of any type of cell is affected by multiple external and internal factors (e.g., nutrition, gene expression, etc.). thus, if this is what Applicant intends by the term "multifactorial" as it applies to cells, the metes and bounds of the term still cannot be determined, since it is not clear how the term defines a subgenus of cells distinct from the other types of cells recited in the claims.

At p. 20, Applicant again refers to the Merck reference and the NIH publication. These arguments are not persuasive for reasons of record.

Applicant turns to Caplan 1991 again and argues that Caplan 1991 teaches that MSC are lineage-nonspecific. Applicant argues that it is patently clear that those skilled in the art understand the term "non-specific" when applied to cells such as stem cells as meaning that the cells are lineage-nonspecific and can develop into a variety of tissues. Applicant urges that for the examiner to deny this alleged fact requires a denial of pure science. This has been fully considered but is not found to be persuasive. The specification does not support this definition. That is, the specification as originally filed does not make it clear that "non-specific" as it applies to cells means that the cells have non-specific *lineages*.

Beginning at p. 21, Applicant addresses the examiner's concerns regarding the contradiction of claims 383, 384, 391, 393, and 394. In this section, Applicant asserts that it is a well-known and well-established fact that not all stem cells are multifactorial and non-specific, and that any skilled person in the medical art would readily understand and agree with such alleged fact. This has been fully considered but is not found to be persuasive for two reasons. First, it is an allegation completely unsupported by any evidence. Furthermore, it is in direct contradiction with the specification which states, "Multifactorial and nonspecific cells (such as stem cells and germinal cells)...." This implies that all stem cells are multifactorial and nonspecific. If Applicant intended that only some stem cells are multifactorial and nonspecific, wouldn't the specification

have stated, "Multifactorial and nonspecific cells (such as **some** stem cells..." or "Multifactorial and nonspecific cells (such as **certain** stem cells..."?

Applicant also argues at p. 22 that not all stem cells result in morphogenesis. This has been fully considered but is not found to be persuasive as it further confuses the issue. The specification does not tie the term "multifactorial and non-specific" to morphogenesis.

For the reasons set forth above, and upon a fresh consideration of the totality of the evidence, the preponderance of the evidence supports the rejection.

New Rejections, Necessitated by Amendment

35 U.S.C. § 112, First Paragraph – New Matter

Claim 404 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. New claim 404 recites administration to a damaged site in a leg of a patient. No support for this limitation could be found in the specification as originally filed. Example 18 of the specification discloses administration of DNA to a damaged artery in a leg. However, a damaged *artery* in a leg is not of the same scope as damaged *site* in a leg, since a damaged site encompasses damaged muscle, damaged bone, damaged skin, etc.

Furthermore, this section of the specification does not envision administration of *cells* at the damaged artery.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 382-405 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure enables one skilled in the art to make and use the claimed invention in its full scope without resorting to undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature or complexity of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See *In re Wands*, 8 USPQ2d. 1400 (Fed. Cir. 1988).

1) In the instant case, the quantity of experimentation required would be very large. Applicant's attention is directed to pp. 1916 to 1918 of Strauer (of record, 2002, Circulation 106:1913-1918), who review the crucial questions that had to be addressed while designing and realizing their trial of administering stem cells to human patients to produce and integrate soft tissue to achieve repair of damaged heart tissue. These included decisions regarding what cell population to use, what delivery method to use,

and when cells should be transplanted. As can be seen from pp. 1916-1918, these were not simple or routine matters and involved great quantities of experimentation. In fact, one can see that the determinations of these details involved the act of invention. Furthermore, as can be seen in this reference, there is no report of the formation of a bud, which is required by all of the instant claims.

2) The specification provides no guidance along the lines of the details worked out by Strauer. The specification broadly asserts that the administration of cells can achieve diverse effects, including growth of any "hard" tissue or "soft" tissue (p. 20), formation of entire new organs (p. 32) or portions of organs (p. 46), restoration of function in any organ (p. 47), formation of auxiliary organs (p. 49), correction of necrosis (p. 49), replacement of missing limbs or body parts (p. 50), treatment of inflammation (p. 50), correction of musculoskeletal injuries or deficiencies (p. 50), formation of hybrid organs (p. 50), etc. No guidance or details are provided as to *how* to achieve these remarkable effects, most of which have never been achieved in this art to this day. The courts have stated that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997). The courts have also stated that "[t]ossing out the mere germ of an idea does not constitute an enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech Inc. v. Novo Nordisk A/S, *supra*).

3) The specification contains only prophetic examples. In fact, none of the prophetic examples are directed to administration of cells to form a bud and then grow soft tissue. Therefore, there are no examples, working or prophetic, directed to the elected invention.

4) The nature of the invention is highly complex, as evidenced by all of the publications of record, including Strauer. All inventions involving administration of active agents of any kind to a patient to achieve a physiological reaction are complex.

5) The state of the art does not support the claims' requirement that administration of cells can cause a bud to be formed and tissue consisting of desired soft tissue to be grown and integrated into the patient's body. Publications disclosing administration of cellular material (blood transfusions, organ transplants, etc.) can be found. However, no publications regarding formation of a "bud" which grows into only soft tissue have been found. It is noted that the publications and declarations of record in the instant application have been reviewed regarding this issue and also were not found to support formation of a bud which grows only into soft tissue.

6) The level of skill in the art is admittedly high.

7) The invention is unpredictable, as it involves administering active agents to a living patient to achieve a physiological response. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), most chemical reactions and physiological activity involve unpredictable factors. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

8) The breadth of the claims is quite large. The claims are generally directed to methods for producing and integrating tissue consisting of desired soft tissue at a selected site in a body of a human patient comprising placing cells in said body of said human patient, forming a bud, and growing said desired soft tissue. Dependent claims further recite limitations regarding the types of cells to be administered, the route and/or site of administration, and the tissues formed. The claims are quite broad. As Applicant states at p. 23 of the amendment received 03 November 2006, "soft tissue" broadly includes fat, fibrous tissue, blood vessels, and other supporting tissue of the body. At p. 24 of the same amendment, Applicant includes organs as another example of soft tissue. Therefore, the claims also encompass growth of neurological tissue (such as brain), heart, lung, pancreas, liver, kidney, etc. Regarding the cells to be administered, there is a question regarding the scope of the various cell types recited in the claims (see rejection under 35 U.S.C. § 112, second paragraph, above). However, the broadest claims recite administration of "cells" without reciting limitations as to type. Therefore, the claims are very broad with respect to the agent being administered and the effect achieved.

Thus, despite the high level of skill in the art, due to the large quantity of experimentation necessary to determine how to effectively administer cells to achieve formation of a bud followed by growth and integration of a tissue consisting of a desired soft tissue, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the effects of

an agent on a physiological response, and the breadth of the claims as discussed above, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number

is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

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ELIZABETH KEMMERER
PRIMARY EXAMINER